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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,822	10/16/2003	Manisha Sharadchandra Deshpande	RELIA.P-113	8483

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	PAPER NUMBER
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,822	DESHPANDE ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,15,17-19,21,24,26-32 and 35* is/are pending in the application.

4a) Of the above claim(s) *1,2,5,15,17-19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26-32 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/08/2007 has been entered.

Status of claims

Claims 24, 26-32 and 35 as amended (3/29/2007) are under examination in the instant office action.

Claims 1, 2, 5, 15, 17-19 and 21 were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions. Applicant timely traversed the restriction requirement in the reply filed on 1/23/2006.

Claims 3, 4, 6-14, 16, 22, 23, 25, 33 and 34 were canceled by applicants.

Claim Rejections - 35 USC § 112

Indefinite

Claims 24, 26-32 and 35 as amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 as amended is rendered indefinite by the presently claimed term "unified" in the lack of definitions in the as-filed specification. The as-filed specification lacks the literal support for this term. The meaning of this term is not described and/or discussed in the as-filed

specification. It is unclear what is intended as "unified" construct. Does it mean that all cells are identical? Does it mean that all cells regardless their morphological and functional characteristics are in one cell lump? By what are cells "unified"? Would be a culture vessel "unifying" component of the claimed composition? What is a nature of the unifying connection as intended? It appears from the as-filed specification that dermal fibroblast cell mass or cell layer (claim 27) is collected from the bottom of the culture plate with a help of a fibrin glue adhesive (page 23, last par.). Does it mean that "unified" feature is some sort of adhesive tape or a matrix or scaffold? Yet, the claim 24 specifically excludes the use of a matrix or scaffold.

The structural and functional characterization of the claimed "tissue like organization of cells" is indefinite as claimed. The "tissue-like organizations of cells" are broadly described by applicants as "living, cellular, tissue substitutes" (page 13, last par.). The presently claimed product is presented in a form of a product-made-by-process. However, the final structure of the claimed product resulting from the manipulation steps are not clearly pointed out. For example: in claim 24 it is unclear whether "a culture vessel" remains in the final product as some "unifying" component of the claimed product, for example: see claim 31. Claims 28 and 31 recite the starting cell seeding densities but the final cell mass in the product-made-by-process is not characterized. With respect to the claims 26 and 30 it is uncertain what components are included in the final product and what components are excluded from the final product since claim 30 recites that cells are grown in a serum containing medium but claim 26 excludes "chemicals" and "growth factors" that are within the serum.

Thus, the metes and bounds of the claims cannot be determined.

New matter

Claims 24, 26-32 and 35 as amended are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation "unified" has no support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of a generic disclosure, nor are there specific examples of the newly limited species that would show possession of the concept of "unified" construct of tissue-like organization of cells free of scaffold or matrix.

The as-filed specification lacks the literal support for this term. The meaning of this term is not described and/or discussed in the as-filed specification. It is unclear what is intended as "unified" construct for the claimed invention.

With respect to exemplified applicants' disclosure it appears that dermal fibroblast cell mass is formed as a layer or sheet-like mass on the bottom of the culture plate (figure 1a) and it is further collected from the bottom of the culture plate with a help of a fibrin glue adhesive as a cell mass attached to an adhesive sheet (page 23, last par.). However, the claim 24 specifically excludes the use of any unifying aid materials. The structural and functional organization of cells in the cell mass sheet-like layer formed at the bottom of the plate is not described in order to determine what feature "unified" the cells.

Thus, there is no sufficient support for the newly inserted term "unified" as described to reasonably convey the meaning of newly inserted term "unified" construct to one skilled in the art. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of term "unified" is considered to be the insertion of new matter for the above reasons.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24, 26-32 and 35 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,755,814 (Berg et al.).

Claims are directed to a 3-dimensional cell mass or a 3-dimensional tissue-like preparation of cells wherein the cells have been grown in the absence of matrix or scaffold. Some claims are further drawn to the cells being dermal fibroblasts. Some claims are further drawn to the use of cells that have been grown in a basic serum supplemented medium in a static culture vessel at initial cell density of $3x10^{5}$ cells/cm^2 for 4 hours.

US 5,755,814 (Berg et al.) discloses a preparation of dermal fibroblasts grown in a simple static culture vessel using a basic DMEM supplemented with serum and in the absence matrices for 4 hours (col. 9, lines 38-46). The cited patent teaches that fibroblasts attached to plastic

dishes and proliferated better without matrices than fibroblasts in the presence of matrices. The cultured dermal fibroblast preparation grown as a sheet-like uniform layer of cells on plastic surface of the culture dish without matrices is considered to be the same cell preparation as the presently claimed "tissue-like organization of cells" within the meaning of the claims and in the light of specification. The fibroblasts are seeded at starting density of $3x10^5$ cells per a well having at least 0.9 cm diameter (col. 9, line 41) and thus, the final cell mass has a diameter of at least 3 mm and more within the meaning of the claims. Considering the disclosed diameter of 0.9 cm (col. 9, line 41) the cells density per cm^2 would be about 4.8×10^5 cells/cm^2 [3×10^5 cells/0.63 $cm^2 = 4.8 \times 10^5$ cells/cm^2, wherein $\pi r^2 = 3.14x(0.9cm/2)^2 = 0.63$ cm^2].

Therefore, the cited patent US 5,755,814 (Berg et al.) anticipates the claimed invention.

Claims 24, 27 and 30-32 as amended remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Furukawa et al. ("Formation of human fibroblast aggregates (spheroids) by rotational culture". Cell Transplantation. 2001, Vol. 10, pages 441-445.).

Claims are directed to a 3-dimensional cell mass or a 3-dimensional tissue-like preparation of cells wherein the cells have been grown in the absence of matrix or scaffold. Some claims are further drawn to the cells being dermal fibroblasts. Some claims are further drawn to the use of cells that have been grown in a basic serum supplemented medium at initial cell density of $3x10^5$ cells/cm^2.

The reference by Furukawa et al. discloses a tissue-like organization of cells that are three-dimensional fibroblast aggregates obtained by growing cells in suspension of high initial seeding density in a culture vessel with 35 mm diameter. The cited preparation of cells are made

without scaffold or matrix requirements within the meaning of the claims. Thus, the cited preparation of cells as a whole cell mass within one culture vessel or as a single cell aggregate is a "3D unified construct" within the broadest meaning of the claims. The reference describes that cell preparation is made by inoculating 5 ml suspension with $1.66x10^6$ cells/ml into a dish having diameter 35 mm and, thus the seeding density is $1.5x10^6$ cells/cm^2 that is calculated as follows: 5 x $1.66x10^6/5.4$ $cm^2=1.5x10^6$ cells/cm^2 , wherein $\pi r^2=3.14x(3.5cm/2)^2=5.4$ cm^2. The presently claimed invention encompasses the use of initial seeding density of $3x10^5$ cells/cm^2 of a culture vessel. Thus, the initial seeding density of the cited cell preparation falls within the claimed range.

Although the cited reference describes that fibroblast cells are grown in a rotating culture vessel, the final product is 3-dimentional tissue-like organizations of cells as required by the claimed invention. Although the cited reference describes that fibroblast cells are grown on medium with supplements including insulin, dexamethasone, etc. the final product as claimed does not exclude the supplements described in the cited reference. Moreover, the final components of the claimed product are not defined by the claimed invention. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. MPEP 2113.

Thus, the 3-dimentional tissue-like dermal fibroblast aggregates disclosed by Furukawa et al. are identical to the claimed tissue-like organization of cells made from dermal fibroblasts.

Therefore, the cited document anticipates the claimed invention.

Claims 24, 26-32 and 35 as amended are rejected under 35 U.S.C. 102(b) as being anticipated by US 6,197,586 (Bhatnagar et al.).

Claims are directed to 3-dimensional tissue-like cell construct wherein the cells have been grown in the absence of matrix or scaffold in high cell density and in high cell seeding density. Some claims are further drawn to the cells being dermal fibroblasts. Some claims are further drawn to the use of cells that have been grown in a basic serum supplemented medium in a static culture vessel at initial cell density of $3x10^5$ cells/cm^2.

The cited US 6,197,586 discloses a 3-dimensional tissue-like cell construct such as dermal fibroblast cells grown in high density micromass cultures that are not treated with external agents (lactate or staurosporine), for example: see at col. 6, lines 25-29 and lines 47-49 or col. 7, lines 33-34. These cells do not differentiate and abundantly stain by type I collagen (col. 11, lines 22-26) as supposed for dermal fibroblast organization of cells and in view of the applicants' disclosure (page 21, par. 1). Thus, untreated dermal fibroblast cell culture remains a "single" tissue "unified" by its morphological and functional features. The cited US 6,197,586 clearly states that untreated dermal fibroblast micromass cultures form a sheet-like organization of cells (col. 12, line 24). Therefore, the cited document anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24, 26-32 and 35 as amended are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,755,814 (Berg et al.), US 6,197,586 (Bhatnagar et al.) and Furukawa et al. ("Formation of human fibroblast aggregates (spheroids) by rotational culture". Cell Transplantation. 2001, Vol. 10, pages 441-445.).

Claims are directed to a 3-dimensional unified construct comprising a single unified tissue-like organization of cells wherein the cells have been grown in the absence of matrix or scaffold. Some claims are further drawn to the cells being dermal fibroblasts. Some claims are further drawn to the use of cells that have been grown in the absence of additional external agents that would influence 3D organization and/or in a basic serum supplemented medium. Some claims are further drawn to the use of cells that have been grown in a static culture vessel. Some claims are further drawn to the use of cells that have been grown at initial cell density of $3x10^5$ cells/cm^2. Some claims are further drawn to the use of cells that have been grown for at least 4 hours. Some claims are further drawn to the cell construct in a form of sheet. Some claims are further drawn to the intended use as a tissue equivalent.

US 5,755,814 (Berg et al.) discloses a preparation of dermal fibroblasts grown in a culture vessel in a basic DMEM supplemented with serum and in the absence matrices (col. 9, lines 38-46) at seeding density of 4.8×10^5 cells/cm^2 as explained above. The final matrix-free cell preparation on the bottom of the plate well is a 3D unified cell construct within the meaning of the claims and when read in the light of specification. In addition, the cited US 6,197,586 teaches that dermal fibroblast cells, that are grown in high density micromass cultures and that are not treated with external agents, do not differentiate and abundantly stain by type I collagen (col. 11, lines 22-26) as supposed for dermal fibroblast organization of cells. Thus, untreated

dermal fibroblast remain a "single" tissue "unified" by its morphological and functional features. The cited US 6,197,586 further teaches that untreated dermal fibroblast micromass cultures form sheet-like organization of cells (col.12, line 24).

The dermal fibroblasts discloses by US 5,755,814 (Berg et al.) and by US 6,197,586 (Bhatnagar et al.) form 3d sheets of unified single tissue cells at the bottom of the culture wells. Further, the reference by Furukawa et al. teaches inoculation of dermal fibroblast aggregates that are initially grown in the absence of matrix into/onto the sheets of biodegradable polymer materials (page 444, col. 2, last par.).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to combine matrix materials with the cell mass grown at high density in the absence of matrix with a reasonable expectation of success in obtaining tissue-engineered dermal grafts suitable for wound healing as taught and/or by Furukawa et al. (page 445, col.1, line 1). One of skill in the art would have been motivated to modify diameter of cell preparations depending on dimension of implantation site of the cell graft, for example.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 3/29/2007 have been fully considered but they are not found persuasive.

With regard to the cited patent US 5,755,814 (Berg et al.) applicant' main argument is that the cells are grown as "monolayer" but not as 3D sheet-like organization of cell formation (response page 8 and page 13). Upon review it is not found true because the cited patent uses the term "monolayer" only when it refers to epidermal cells grown on a composite matrix of insoluble collagen and fibroblasts cells, for example: see at col. 2, lines 41-43 and at col. 14, line 62). The teaching relied upon for the instant claim rejection is an embodiment describing dermal fibroblasts grown at high seeding cell density without matrices (col. 9, lines 38-47). The cells and manipulations for growing cells are identical as disclosed by US 5,755,814 and as required by the claimed invention. Thus, the final structure of the product obtained as result of culturing the same cells under identical conditions are identical within the meaning of the claims and when read in the light of specification. Applicants also argue that the cell preparations disclosed by US 5,755,814 is made by using a different cell seeding density. Upon review of the reference it is not found true, for example: see calculations as explained above. A culture well described by US 5,755,814 has 0.9 cm diameter (see col. 9, line 41) but not the diameter of 1.5 cm as argued (pages 13-14).

With regard to the cited reference by Furukawa et al. applicants argue that the cited cell preparations are small aggregates and that they are not a unified sheet-like organization of cells (response pages 8-10). Yet, the claimed invention (claim 24) is not limited to a sheet-like organization of cells as argued. Applicants further argue that the culture vessel contains a suspension of cell aggregates and, thus, not all cells seeded in a culture vessel are incorporated in a final 3D unified construct. However, a single dermal fibroblast 3D cell aggregate disclosed by Furukawa et al. anticipates the claim 24 because the culture vessel is not a component of the

claimed product and the number of cells in the final product is not limited by the claims. Although the cited reference describes that fibroblast cells are grown on medium with supplements including insulin, dexamethasone, etc. the final product as claimed does not exclude the supplements described in the cited reference. Moreover, the final components of the claimed product are not defined by the claimed invention.

Product-by-process claims are not limited to the manipulations of the recited steps, only the final structure implied by the steps. MPEP 2113.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

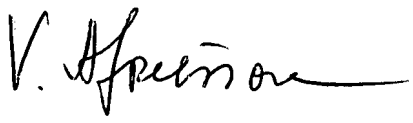
The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1657

April 26, 2007



VERA AFREMOVA

PRIMARY EXAMINER